

# PATENT SPECIFICATION

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## COMPLETE SPECIFICATION

### NO DRAWINGS

### Process for the Manufacture of 2-Amino-aldohehexoses

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention provides a process for the manufacture of 2-amino-aldohehexoses, for example glucosamine and salts thereof.

2-Amino-aldohehexoses are valuable intermediate products. 2-Amino-aldohehexoses, for example, can be converted by the process described in Application No. 38761/56 (Serial No. 832,080) by treatment with suitable acylating agents into therapeutically valuable N-acylamino-sugars, such as for example N-nicotinoyl-D-glucosamine.

The invention is based on the unexpected observation that 2-amino-aldohehexoses and acid addition salts thereof can be obtained in good yield by reacting a 1-amino-2-ketohehexose with anhydrous liquid ammonia, hydrolysing the resulting 1-imino-compound, and if desired, converting the 2-amino-aldohehexose so obtained into an acid addition salt thereof. The starting materials are known or can be made by methods in themselves known.

There may be used, for example, 1-amino-fructose, 1-amino-sorbose or 1-amino-tagatose, the hydroxyl groups of the sugar residue being unsubstituted or one or more of the said groups may be substituted, for example, acylated, e.g. acetylated. They can be obtained in excellent yield from the corresponding aldoses, for example D-glucose, by means of the Amadori reaction (M. Amadori, Chem. Zbl. 32/II, 33 (1929)). 1-Amino-2-ketohehexoses in which the amino group is unsubstituted are obtained by treating an aldohehexose with a bis-arylmethyl-

amine and subsequent hydrogenolytic cleavage of the resulting 1-(N,N-bis-arylmethylamino)-2-ketohehexoses according to Application No. 2005/57 (Serial No. 833,263). The decomposition of the imino-compounds may be carried out in known manner, for example, in the presence of water or an ammonium salt or inorganic or organic acid.

The reaction may be carried out in a manner in itself known in the presence or absence of a condensing agent and/or a catalyst at room temperature or at a raised temperature in an open vessel or a closed vessel.

Depending on the procedure used the 2-amino-aldohehexoses are obtained in the form of their bases or salts. From the salts there can be obtained in a manner in itself known the free amine bases. From the bases, acid addition salts can be obtained by reaction with acids, for example, hydrohalic acids, sulfuric acid, nitric acid, phosphoric acid, thiocyanic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, malic acid, methane sulfonic acid, ethane sulfonic acid, hydroxyethane sulfonic acid, benzene or toluene sulfonic acid.

The following Examples illustrate the invention:

#### Example 1

1.2 grams of the acetic acid addition salt of 1-amino-1-desoxy-D-fructose (iso-glucosamine, D-fructosamine) are treated in a V<sub>2</sub>A-autoclave with 30 cc of dry liquid ammonia for 6 hours at 95-105°C under a pressure of about 36-39 atmospheres (gauge pressure). The ammonia is then slowly evaporated, and the residue is dissolved in a small amount of 0.1N-hydrochloric acid and adsorbed on 30 grams of ion-exchanger (Amberlite JR 120 [Registered Trade Mark], in the H-form). The adsorbent is rapidly washed with water and then the product is

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eluted with 50 cc of 1N-hydrochloric acid. The eluate is evaporated in vacuo, the residue so obtained is dissolved in a small amount of water, and the solution is mixed with alcohol. 0.5 gram of D-glucosamine hydrochloride crystallises. Its identity with glucosamine from the shells of lobsters is determined by paper chromatography and preparation of the phenyl-isocyanate compound (H. Steudel, Z. physiol. Chem. Vol. 33, page 223, 1901).

#### Example 2

4.8. grams of the acetic acid addition salt 1-amino-1-desoxy-D-fructose are kept in 40 cc of anhydrous liquid ammonia for 3 days at room temperature. The ammonia is then evaporated in vacuo whilst carefully excluding moisture. The residue is dissolved in 50 cc of 1N-hydrochloric acid and kept for one hour on a steam bath. The solution is clarified with animal charcoal and then evaporated in vacuo. The residue is dissolved with a little water and mixed with a large excess of alcohol. 2.3 grams of D-glucosamine hydrochloride crystallise.

#### WHAT WE CLAIM IS:—

1. A process for the manufacture of 2-

amino-aldohehexoses and acid addition salts thereof, wherein a 1-amino-2-ketohexose is reacted with anhydrous liquid ammonia, the resulting 1-imino-compound is hydrolysed, and, if desired, the 2-amino-aldohehexose so obtained is converted into an acid addition salt thereof.

2. A process as claimed in claim 1, wherein 1-amino-1-desoxy-D-fructose is used as starting material.

3. A process for the manufacture of a 2-amino-aldohehexose or an acid addition salt thereof conducted substantially as described in Example 1 herein.

4. A process for the manufacture of a 2-amino-aldohehexose or an acid addition salt thereof conducted substantially as described in Example 2 herein.

5. 2-Amino-aldohehexoses and acid addition salts thereof, whenever made by the process claimed in any one of the preceding claims.

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